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Brief communication

Clinical characters and treatments of retinal vasoproliferative tumors

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ABSTRACT

Retinal vasoproliferative tumors (VPT) are uncommon benign vascular tumors. They mostly occur in healthy patients, but may be associated with other chorioretinal diseases. Here we report four patients with VPT at a referral center from 2006 to 2015. Three patients denied any past history and one had a history of retinal detachment surgery. VPT-related complications included epiretinal membrane (ERM) ($n = 2$), cystoids macular edema ($n = 1$), and lamellar hole combined with dense cataract, rigid anterior capsule and vitreous opacity ($n = 1$). Treatments for VPT and comorbidities included vitrectomy (VT) and membrane peeling with tumor resection ($n = 2$), a combined treatment of photodynamic therapy (PDT) and intravitreal injection (IVI) of anti-vascular endothelial growth factor (anti-VEGF) ($n = 2$). Tumor shrinkage was achieved in both patients treated with PDT and IVI of anti-VEGF injection. The other two patients with ERM were successfully treated with VT and tumor resection. Visual acuity improved at least two lines in three patients, and one patient had decreased vision due to cataract formation after VT. Pathology of the resected tumor in one case revealed massive gliosis with positive stain of vascular endothelial cells and glial fibrillary acidic protein stain. Yet the peeled membrane was acellular. Possible beneficial treatments for VPT and comorbidities include PDT combined with IVI of anti-VEGF, or VT and membrane peeling with tumor resection.

1. Introduction

Retinal vasoproliferative tumors (VPT) are rare, unilateral and benign retinal vascular tumors. They are yellowish-red tumors, and are mostly located on the inferotemporal peripheral retina. Unlike the retinal hemangioblastoma, VPT rarely have dilated and inflamed feeder or drainage vessels, and they demonstrate a paucity of microvessels yet a preponderance of gliosis.[1]

VPT mostly occur in middle-aged patients who are healthy (primary VPT), or they may be associated with other chorioretinal diseases such as uveitis, retinitis pigmentosa, and Coats' disease. They may also occur after retinal detachment surgery (secondary VPT).[2–6] Most patients suffer from visual symptoms that are secondary to leakage and inflammation of this peripheral vascular tumor, such as decreased vision, floater, distortion, or photopsia.[7,8] Without dilating the pupil and checking the peripheral retina, the VPT might be missed. Visual acuity (VA) varied from light perception to 6/6, depending on the complications of VPT.[7,8] The clinical course was generally insidious and slow but exudative retinal detachment with macula involvement or neovascular glaucoma has been reported.[8,9]

To the best of our knowledge, only one case of VPT has been orally presented at the annual meeting of the Taiwan Ophthalmology Society in 2013 by Chu & Wang, and another possible case of VPT has been published in one report.[10] In this study, we report four cases of VPT. Two patients had more than 8 years of follow-up. The clinical presentation, treatment and outcome, as well as the histopathology of the tumor are described.

2. Case reports

Four patients with VPT were recruited following a chart review from 2006 to 2015. Three healthy females with an average age of 49 years had primary VPT without prior ocular history or surgery. One 84-year-old male had a history of retinal detachment surgery. Initial best-corrected VA was less than 6/12 in all patients (average Snellen acuity of 6/24). After fundus examination, two patients had a yellowish-red tumor at the temporal lower periphery (primary

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VPT), one at the nasal lower periphery (primary VPT), and one at the temporal upper periphery (secondary VPT) (Table 1).

2.1. Case 1

In 2006, a 41-year-old female presented with blurred vision in the left eye. The rapid and dense epiretinal membrane (ERM) was noted just 3 weeks after her first visit (Figure 1). VA also dropped from 6/7.5 to 6/60. Due to a progressive thickening of the ERM and worsening VA, we promptly performed vitrectomy (VT), membrane peeling, and external tumor resection. VA improved to 6/8.6 in 6 months after surgery and this was maintained for 6 years until the last visit.

2.2. Case 2

This was an 84-year-old male with a history of retinal detachment surgery and cataract surgery 3 years previously. The tumor was located at the border of an old chorioretinal scar at the temporal upper periphery on the left eye (Figure 2). Cystoid macular edema was found on optical coherence tomography (OCT). He received three intravitreal injections (IVI) of bevacizumab and two treatments of photodynamic therapy (PDT). As a result, the tumor shrank and the macular was flat. VA improved from 6/15 to 6/10 and was maintained for 6 years.

2.3. Case 3

Case 3 was a 58-year-old female with VA of 6/30 in her right eye. A slit-lamp examination showed a dense cataract. Indirect ophthalmoscopy revealed VPT with lipid exudate, vitreous opacity with fibrin sheet, and lamellar hole (Figure 3). She also received IVI of ranibizumab (twice) and PDT (once). We then performed phacoemulsification and intraocular lens implantation 9 months after the PDT. A very rigid and resistant anterior capsule was found during the cataract surgery. After 1 month, severe anterior capsule contraction was noted. Following neodymium-doped yttrium aluminum garnet (Nd:YAG, Lightex Inc) laser anterior capsulotomy, the VA improved to 6/10.

2.4. Case 4

A 48-year-old female presented with blurred vision of the right eye. VPT and ERM were diagnosed, and two treatments of IVI of ranibizumab and one of PDT were carried out before the planned surgery in order to shrink the tumor. Six weeks after PDT, we performed VT, membrane peeling, and tumor resection (Figure 4). To avoid intraoperative bleeding, under general anesthesia, systolic blood pressure was controlled between 80–100 mmHg during the procedure of tumor resection. The tumor was located by indirect ophthalmoscopy and a 6×4 mm sclera lamellar flap was made. Diathermy was carried out on the margin of the exposed choroid under the deep scleral flap with careful cauterization to reduce bleeding, followed by resection of the choroid and the tumor with scissors, along with the deep scleral flap. The superficial scleral flap was covered back and sutured, with additional transscleral cryotherapy along the scleral flap. VT was then performed. During the VT, no posterior vitreous detachment (PVD) was found and the ERM was adherent to the posterior hyaloid membrane. After carefully isolating and removing the ERM, the underlying internal limiting membrane (ILM) was found to be intact and was subsequently

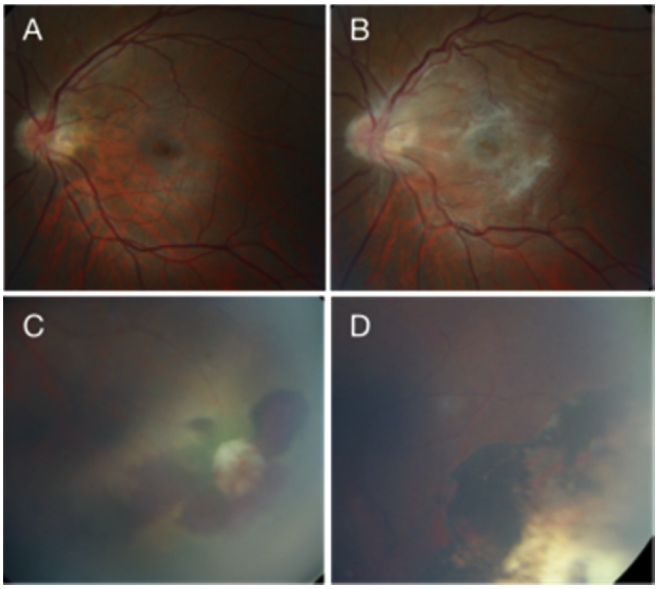

Fig. 1. Color fundus of Case 1 (A) at presentation; (B) rapid and dense ERM occured after 3 weeks; (C) VPT with retinal hemorrhage and pigmented retina change; and (D) disapperance of tumor with chorioretinal scar after VT, membrane peeling, and tumor resection. ERM = epiretinal membrane; VPT = vasoproliferative tumor; VT = vitrectomy.

Table 1
Demographic and clinical data of the four patients with VPT.

	Case			
	1	2	3	4
Age	41	84	58	48
Gender	F	M	F	F
Eye	OS	OS	OD	OD
Location	Inferotemporal	Superotemporal	Inferotemporal	Inferonasal
Previous history	Nil	RD surgery	Nil	Nil
Initial VA	6/60	6/15	6/30	6/12
Complication	ERM	Cystoid macular edema	Lamellar hole, dense cataract with rigid anterior capsule and vitreous opacity	ERM
Treatment	VT + MP + tumor resection, Phaco-IOL	PDT + IVI of bevacizumab	PDT + IVI of ranibizumab, Phaco-IOL	PDT + IVI of ranibizumab, VT + MP + tumor resection
Follow-up time	9 years	8 years	10 months	7 months
Final VA	6/8.6	6/10	6/10	6/15

ERM = epiretinal membrane; IVI = intravitreal injection; MP = membrane peeling; PDT = photodynamic therapy; Phaco-IOL = phacoemulsification and intraocular lens implantation; RD = retinal detachment; VA = visual acuity; VT = vitrectomy.

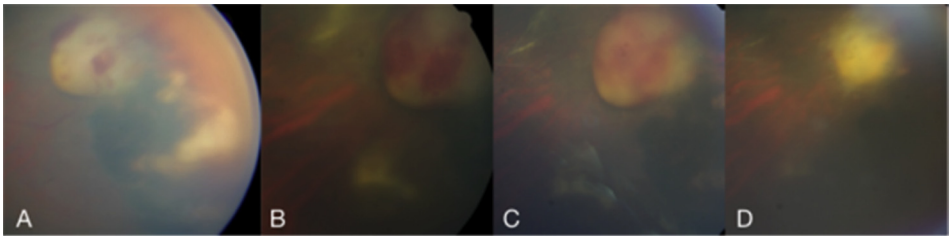

Fig. 2. Color fundus of Case 2 (A) at presentation; (B) 1.5 years after first IVI of bevacizumab; (C) 1 month after second IVI of bevacizumab and first PDT; and (D) 4 months after third IVI of bevacizumab and second PDT. IVI = intravitreal injection; PDT = photodynamic therapy.

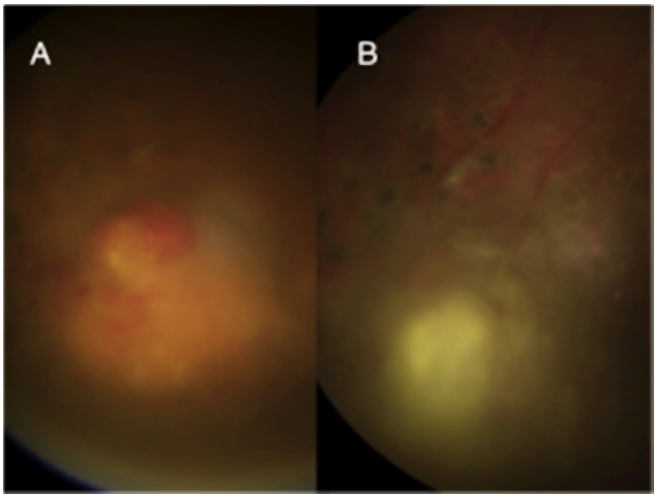

Fig. 3. Color fundus of Case 3 (A) at presentation; and (B) 9 months after first PDT and second IVI of ranibizumab. IVI = intravitreal injection; PDT = photodynamic therapy.

peeled at the macular area. Endolaser was performed to confine the shallow retinal detachment alongside the resected tumor. Pathology of the resected tumor revealed massive gliosis with a positive CD31 stain of vascular endothelium, and a positive of glial fibrillary acidic protein (GFAP). Pathology of the peeled membrane showed acellular membrane without glial cells or fibroblasts. The postoperative vitreous hemorrhage cleared up in 2 months following two treatments of fluid gas exchange. The VA of the final follow up 4 months later was 6/15 due to cataract.

Table 1 summarizes the demographic and clinical data of the four cases with VPT. The associated complications included ERM ($n = 2$), lamellar hole ($n = 1$), cystoid macular edema ($n = 1$), and dense cataract with rigid anterior capsule and vitreous opacity ($n = 1$). Treatments included VT and membrane peeling with tumor resection ($n = 2$), combined therapy of PDT and IVI of anti-vascular endothelial growth factor (VEGF) ($n = 2$). Tumor shrinkage was achieved in all patients treated with PDT and IVI of anti-VEGF. VA improved at least two lines in three patients, and one had decreased vision (6/12 to 6/15) due to cataract formation after VT (Case 4).

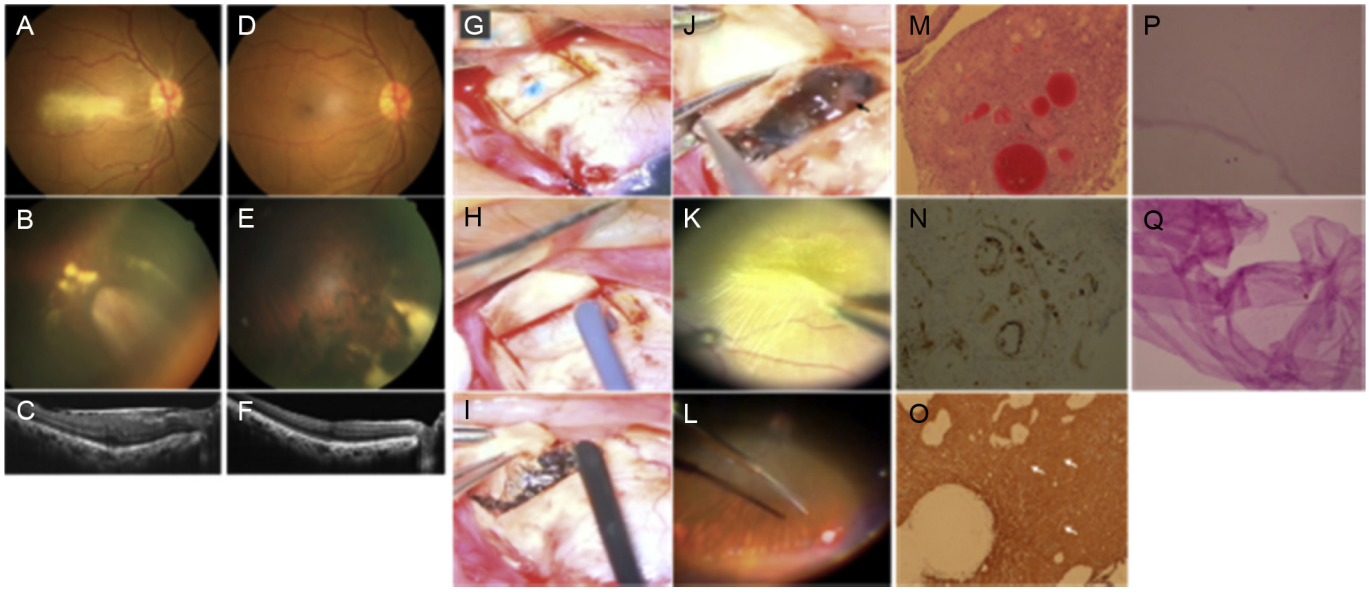

Fig. 4. Color fundus of Case 4 (A) at presentation with ERM; (B) tumor at nasal lower periphery; and (C) retinal edema with ERM in OCT. (D) Color fundus after VT, membrane peeling, and tumor resection showed flat macular; (E) laser scar and absence of tumor; and (F) normalized macular thickness in OCT. (G) A 6 × 4 mm sclera lamellar flap was made to cover the tumor (blue dot); (H) followed by diathermy on the margin of the deep scleral flap; and (I) diathermy on the margin of the exposed choroid along with the scleral flap. (J) Tumor (arrow) exposure and resection; (K) peeling of ERM, after VT; and (L) endolaser to confine the shallow retinal detachment alongside the resected tumor. (M) Massive gliosis in H&E stain of the resected tumor. (N) Proliferated endothelial cells of blood vessels in CD31 stain. (O) Highly elongated fibrous astrocytes (arrows) in GFAP stain. (P) The pathology of the peeled membrane showed scant cells. (Q) The pathology of ILM revealed hypocellular membrane with homogeneous cell distribution, low cellularity of glial cells and few fibroblasts. ERM = epiretinal membrane; GFAP = glial fibrillary acidic protein; ILM = internal lifting membrane; OCT = optical coherence tomography; VT = vitrectomy.

3. Discussion

We presented four cases with VPT which was the largest study of VPT reported in Taiwan. We found that the most unique feature was rapid progression of ERM and decreased VA.

Idiopathic ERM is mostly associated with increased age and PVD.[11] VA can remain stable for years, compared to VPT-related ERM with rapidly worsening VA. Previous reports of VPT complicated with ERM showed a mean of 5 months duration between the time of developing visual symptoms and the diagnosis of VPT.[12] In our study, the two cases with complicated ERM (Case 1, Case 4) were younger and had visual loss due to rapid ERM formation in an average of 5 weeks (4 weeks, and 6 weeks). In addition, there was no PVD during VT in these two cases. The histopathology of the ERM in Case 4 showed minimal cellularity, which was not common in idiopathic ERM where glial cells and myofibroblasts proliferated.[13] The peeled ILM, however, showed greater cellularity than the overlying ERM. We presumed that the mainly collagen fibers of the ERM was actually the localized contracture of the posterior hyaloid membrane. It was unknown how the VPT can induce the contracture of collagen fibers without cellular reaction.

VPT-related complications of the anterior segment were rarely reported. The most common anterior segment complication in eyes with VPT was glaucoma.[7] One patient had complicated neovascular glaucoma due to peripheral anterior synechia and neovascularization in the iris and angle.[9] After receiving VT and tumor resection, the intraocular pressure was normalized.[9] Another two cases with ocular hypertension were treated with topical antiglaucoma medications and Ahmed valve implantation respectively.[7] In Case 3 there was posterior segment findings of retinal lipid exudate, fibrinous reaction and lamellar hole. Dense and rigid anterior capsule was also found during cataract surgery. Rapid anterior capsule phimosis developed within 3 weeks after cataract extraction. The fibrous contracture of the lens capsule was similar to the development of ERM formation in Cases 1 and 4. It will be interesting to examine the removed lens capsule to see if there is any difference between the capsule and removed ERM.

The current managements for VPT include observation, cryotherapy, laser photocoagulation, PDT, plaque brachytherapy, and IVI of anti-VEGF or dexamethasone implant. Photocoagulation alone does not change the tumor lesion nor improve subretinal fluid on OCT.[14,15] IVI of bevacizumab alone can improve VA, but without significant difference and does not last long.[16,17] PDT alone shows successful regressions of tumors. [14,18] However, intraretinal and subretinal exudation may increase because of the inflammation and vaso-occlusive effects for PDT. [14,18] In Case 2, the tumor remained the same size after one dose of IVI. After two sessions of combined PDT plus IVI of bevacizumab, within 2 months the tumor regressed for 6 years. Combination therapy, such as that for the small retinal hemangioblastoma in von Hippel-Lindau disease, is probably one of the best treatment choices for VPT.[19] Two of our cases had VT and tumor resection to remove the tumor and ERM at the same time. One had PDT plus IVI of ranibizumab before the surgery in attempt to decrease the tumor size.

Histopathology of the VPT in Case 4 reveals elongated, GFAP-positive spindle-shaped glial cells, and positive CD31/CD34 of the vascular component without mitotic appearance, which was similar to previous reports.[1,8] VPT is also called reactive retinal astrocytic tumor because of the small number of microvessels with a very low proliferation index, such as Ki67 staining (cell replication indicator).[1] However, they still provide some capacity to damage retina or other intraocular tissue due to secondary exudation or inflammation. The acellular fibrous membrane in our ERM specimen and the lens capsule thickening in another case might indicate that the VPT can probably actively secrete factors to enhance fibrous tissue proliferation.

The VPT shares similar fundus appearance with other retinal vascular tumors, such as retinal hemangioblastomas with or without von Hippel-Lindau disease. Unlike the VPT, hemangioblastomas usually occur at a younger age (10–40 years), with prominent feeding and draining vessels, and are bilaterally involved with multiple locations. Moreover, retinal hemangioblastoma rarely have the complication of ERM. Patient history of renal cell carcinoma, central nervous system hemangiomas, and other tumors may also provide additional information for suspected von Hippel-Lindau disease.[20]

There are several limitations in this article, including the limited number of cases, absence of tumor size measurement, and lack of histopathology of the lens capsule specimen.

In summary, the most common complication of VPT in our study was the rapid development of ERM. We also found one patient with anterior segment complication. Combination therapy with PDT and IVI of anti-VEGF provided long-term tumor regression and dry macula. VT with membrane peeling and external tumor resection could be another treatment of choice to remove the ERM and tumor together. The clinical spectrum and histopathology in our study suggest that VPT can secrete some factors enhancing the fibrous contracture without many cellular reactions. Correct diagnosis and appropriate treatments are important to halt the progression and complications of VPT.

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